

EXHIBIT B



USP Chapter <797>

Q&A

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Understanding Beyond-Use Dating for Compounded Sterile Preparations

Q: What purpose does the beyond-use date of a compounded sterile preparation (CSP) serve?

A: A CSP’s beyond-use date identifies the time by which the preparation – once mixed – must be used before it is at risk for chemical degradation, contamination, and permeability of the packaging. In other words, the beyond-use date serves to alert pharmacists and caregivers to the time after which a CSP cannot be administered.

Q: What risks are associated with assigning an inappropriate beyond-use date to a CSP?

A: First is the issue of sterility. We certainly want to avoid contamination, so assigning appropriate beyond-use dates limits the possibility of administering a contaminated CSP. Stability is also a factor; after a CSP’s beyond-use date, it could start to precipitate or other chemical reactions could occur.

Q: What’s the difference between a beyond-use date and an expiration date?

A: An expiration date is identified by the product manufacturer. It is placed on the vial and in the package insert, and is dependent on the temperature and the appropriate storage of the unopened container. A beyond-use date is assigned by the pharmacy for a preparation that they compound.

Q: What factors are used to determine a CSP’s beyond-use date?

A: Of the three factors used – stability, sterility, and risk level – you should use the shortest of the beyond-use dates dictated by those factors. People sometimes think, “Well, I read in the literature that this is stable for 30 days,” but that doesn’t mean it’s going to remain sterile for 30 days. So always use the

shorter of the two timeframes to determine your CSP’s beyond-use date.

Q: Does USP provide guidance on beyond-use dates?

A: Yes, and most people use the USP limits to determine their beyond-use dates. You can, however, exceed USP’s recommended beyond-use dates if you have independent sterility testing done, but most people use the USP limits.

Q: When does it make sense to have independent sterility testing done?

A: It makes sense to conduct testing if you want to exceed the limits of the USP sterility times, or if you are making high-risk preparations. Sterility tests are required for high-risk preparations that are made in batches of more than 25 units.

Q: Are there situations in which guidance beyond the USP limits is necessary?

A: In most cases, you can use the limits established by USP. There may be drugs, such as ampicillin, that do not maintain their stability for as long as the sterility limits in USP. For those, you have to use the shorter of the stability and sterility dates. A best approach is to use the USP guidelines and then deal with those unusual drugs individually.

Q: What are some basic guidelines for determining the beyond-use dates for the different CSP risk levels?

A: Simply put, the higher the risk, the less time that you can keep a preparation. The beyond-use date is usually found by intersecting the risk level and the temperature at which the CSP is being stored. (See Figure 1.) The temperature

Figure 1. In the absence of sterility testing, storage periods should not exceed the following:

Storage Temperatures	Low Risk-Preparations	Medium-Risk Preparations	High-Risk Preparations
Controlled Room Temperature (<25°C/<77°F)	48 hours	30 hours	24 hours
Refrigerator Temperature (2-8°C/36-46°F)	14 days	7 days	3 days
Freezer Temperature (<-20°C/<-4°F)	45 days	45 days	45 days

Source: USP Chapter <797>



<797>

Cleaning Products for Compounded Sterile Preparations (CSPs) USP <797>

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of your refrigerators and freezers needs to be recorded as well to ensure that they maintain the required temperatures.

Q: How can pharmacists ensure the proper storage of their CSPs?

A: The simplest way would be to read and log your refrigerator and freezer thermometers every day. But that just shows one snapshot in time – not what’s happening over the course of the day. Perhaps the most efficient method is to use electronic temperature monitors for logging temperature information. These devices provide a bigger, more complete picture of your storage conditions.

Q: What special considerations must be given to multiple-dose vials?

A: The first printing of USP <797> limited multi-dose vial use to within 30 days of opening the vial. The proposed revisions limit that to 28 days, in concert with other FDA and USP requirements. Some multi-use vials have shorter beyond-use dates, such as some of the new insulins, especially when stored at room temperature. So it is important to check the individual package inserts for expiration date information before assuming you can store something for 28 days.

Q: And are there other dosage forms or particular compounding ingredients that will affect a CSP’s beyond-use date?

A: Anything that gets added to a compound – whether it’s the base solution, diluent, or whatever – could affect the beyond-use date. So you have to check all of the pieces of the puzzle.

Q: What immediate steps can a pharmacy take to improve its policies for beyond-use dating?

A: First, they need to identify the risk levels of the CSPs they are making in their hospital and familiarize themselves with what’s happening in areas outside of the pharmacy, such as obstetrics; the cath lab; critical-care areas, where immediate-use preparations could be mixed; and anesthesia, where they could be making epidural preparations. Second, they need to make sure that no CSPs have been assigned dates beyond the basic risk-level guidelines. Most organizations do not make high-risk preparations; they only make low- and medium-risk preparations.

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That said, if a hospital is compounding high-risk preparations, they need to make sure they are doing so in a USP <797>-compliant area or they should consider outsourcing their high-risk compounding to one of the large compounding pharmacies that meet <797> requirements.

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Q: Are there common misconceptions regarding beyond-use dating that must be dispelled?
A: I think there are two things: First, people try to extend their beyond-use dates by using the longer of the stability or sterility dates. That is bad practice. Second, USP <797> offers beyond-use dating based on the storage of a preparation, and those time limits must include the time taken to mix the compound all the way up to when the infusion begins or the injection is given. There is some confusion about whether or not the beyond-use date includes the time of infusion. It doesn't. USP <797> deals with the time from initial preparation up to the time of administration. ■

Patricia C. Kienle, RPh, assumed her current position with the Cardinal Health Center for Safety and Clinical Excellence in January 2007, after serving as an operations director for Cardinal Health's Pharmacy Management and Medication Solutions businesses. The recipient of an MPA in health service administration from Marywood College in Scranton, Pennsylvania, and a BSc in pharmacy from Philadelphia College of Pharmacy and Science, Kienle has more than 30 years' experience in hospital pharmacy practice.



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